Remarks

Claims 33 and 55 have been amended to correct typographical errors. Claims 33 and 55 have also been amended to incorporate the limitations of original claims 43 or 47, as discussed below, to be specific to the named drugs, and to delete the reference to buccal delivery, now being specific only for sublingual delivery. Claim 41 has been amended into independent form, and claims 51 and 54 amended to depend from claim 41. Claim 34 has been amended to define the active ingredient as that present in the first component.

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 47 and 51 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

A chewable component would be understood by those skilled in the art to be one which is chewed and then swallowed.

Claim 51 now depends from claim 41, which recites drugs having a molecular weight of less than 350 daltons OR as specifically named. Therefore claim 51 further limits the scope of claim 41 as to the embodiment drawn to drugs having a molecular weight of less than 350 daltons.

Rejections Under 35 U.S.C. § 103

Claims 33-43, 45, 47, and 49-57 were rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 5,053,032 to Barclay *et al.* ("Barclay"). Claims 33-43, 45 and 47-57 were

rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 5,702,723 to Griffin ("Griffin"), in view of WO 98/43235 to Telia AB. It appears that the Examiner made a typographical in this rejection. Applicants believe that the rejection is over Griffin, in view of U.S. Patent No. 4,661,492 to Lewis *et al.* ("Lewis"), since the Telia application is drawn to a "Device and Method for Prosody Generation at Visual Synthesis". Claims 44 and 46 were rejected under 35 U.S.C. § 103(a) as being obvious over Griffin, in view of U.S. Patent No. 4,814,181 to Jordan *et al.* ("Jordan"). Claims 33-39 and 42-57 were rejected under 35 U.S.C. § 103(a) as being obvious over GB 800,973 to Sterling Drug, Inc., in view of U.S. Patent No. 4,322,433 to Leslie *et al.* ("Leslie"). Applicants respectfully traverse these rejections to the extent that it is applied to the claims as amended.

The claims as amended now recite either that the two component formulation has a chewable or sustained release second component for oral ingestion following immediate release sublingually of a first component (claims 33 and 55, and claims dependent thereon) or an effervescent first component which is released and absorbed sublingually (claim 44, and claims dependent thereon).

Sublingual release and absorption is quite different from other types of oral delivery. An article from the internet which provides a concise explanation of sublingual absorption and the mechanics thereof is enclosed for the examiner's convenience. A number of factors are critical to the amount of absorption.

The examiner has acknowledged that the prior art does not disclose the subject matter of the claims, but believes the subject matter to be obvious. The standard under 35 U.S.C. 103 for obviousness is quite clear: not only must the references disclose each claimed feature, but the motivation to combine as applicants have done, with a reasonable expectation of success. The motivation must come from the references themselves, not merely an assertion that such a combination would be obvious.

Barclay

Barclay does not disclose the drugs that are claimed, as the examiner has correctly noted. Barclay does not disclose a first component for sublingual administration, only buccal, which is now deleted from the claims. Barclay also does not disclose the use of a sustained release or chewable formulation which is swallowed, nor does he lead one of skill in the art to substitute such formulations for those that he does describe. Barclay describes an osmotic device. Indeed, Barclay teaches away from either sustained release or a chewable second portion. All of the drugs Barclay describes, such as prochlorperazine and nitroglycerine are for immediate release and uptake. The one embodiment with an HOMC coating might delay release of the second component but would not result in sustained release. Chewing would destroy an osmotic device.

Barclay describes a device that is designed to deliver the same drug into the oral cavity and, optionally, into the GI tract – the device has only one drug reservoir (see Fig. 1, 2, 3, 4 and col. 8, lines 31-35). This device cannot be used to deliver two different drugs as described by Hirsh et al. and, therefore, distinctively different.

Barclay's device is "designed to be retained in the mouth for periods on the order of about 0.5 to 12 hours" (col. 7, lines 35-36). Hirsh describes a composition wherein the first component [that contains drug to be absorbed in the mouth into the systemic circulation] "disintegrates or dissolves within 10 minutes, when composition is contacted with saliva" (Claim 48 as submitted). Barclay indeed discloses a variety of drugs that can be delivered using the device (col. 10, line 50 to col. 11, line 35), however, only one drug can be delivered using Barclay's device (see above). The drug could be either one intended for absorbtion within the oral cavity (e.g. nitroglycerine) or drug intended for absorption within the GI tract (e.g. prochlorperazine). Applicants' composition allows for administration of drug intended for absorption within the oral cavity followed by drug intended for absorption within the GI tract.

Applicants select and use the drugs for delivery within the oral cavity based on their ability to be absorbed through the oral mucosa membrane. Barclay makes no distinction between two different classes of drugs: (a) drugs that are released within the oral cavity and absorbed within the oral cavity and (b) drugs that are released within the oral cavity, then swallowed with saliva, and finally absorbed in the GI tract. Applicants have designed a composition that can deliver drugs from both classes in a single dosage form.

Accordingly, nothing in Barclay would lead one skilled in the art to the subject matter of claims 33 and 55, and claims dependent thereon.

Griffin

Griffin teaches "a multi-stage delivery system in the form of a pill having an outer layer comprising an active substance or substance that will dissolve and have a beneficial effect somewhere in the mouth or upper respiratory area with the subsequent layers dissolving and the contained substances acting deeper within the body such as in the gastro-intestinal area or systemically" (col. 3, lines 8-13). Griffin emphasizes the fact that "saliva-soluble" active ingredient of an external layer is "locally acting agent providing a condition-related therapeutic effect in the mouth, esophagus or bronchial tract" (col. 6, lines 33-35). The active ingredient of an internal layer is "internally or systemically active" (col. 6, lines 23-24). Both active ingredients of Applicants' composition are systemically acting agents that are absorbed into the bloodstream at the different sites of the human body: first ingredient within the oral cavity and the second ingredient within the GI tract.

As the Examiner notes, Griffin describes drugs in a coating of HPMC, which would delay release, with an outer coating of a substance that dissolves. "The outer coating can include calcium carbonate". This does not teach a coating that is dissolved and absorbed sublingually. Indeed, as noted in the accompanying article, ability of a drug to be absorbed sublingually depends on its ionization state that is controlled by pH. It is as likely that calcium carbonate would prevent sublingual absorption of many of the disclosed drugs as it is that it would allow sublingual absorption, absent a teaching that the pH must be adjusted appropriately!

Lewis

Lewis merely discloses a particular combination of naltrexone with buprenorphine for parenteral or sublingual delivery. Lewis does not describe a first component which *must* be delivered sublingually and a second which *must be* swallowed, for sustained release, or chewed and swallowed.

There is no teaching that would lead one to substitute the drugs of Lewis for the drugs of Griffin, nor even if they did, would the resulting combination lead to the claimed drug formulation, much less with any reasonable expectation of success. Accordingly, Giffin in combination with Lewis does not make obvious the subject matter of claims 33-43, 45, and 47-57.

Jordan

With respect to claims 44 and 46, Jordan does not make up for the deficiencies of Griffin. Claim 44 requires that the first component be within an effervescent coating that releases drug instantly sublingually. Claim 46 requires a first component formulated for sublingual release in combination with either a chewable or sustained release second component, further including a delayed release coating. Griffin does not lead one skilled in the art to make a formulation containing a first drug that must be delivered sublingually, in combination with an effervescent coating. Indeed, Jordan is such a specialized device, and so different from what is claimed, it is impossible to see how or why anyone would be led to combine any of its disclosure with that of Griffin. The device of Jordan is an osmotic device, like that of Barclay. There is nothing that

would provide for an immediate release of the first component, much less in an effervescent form. Accordingly, claim 44 is not obvious from Griffin and Jordan.

Claim 46 is also not obvious. As discussed above, Griffin does not make obvious claim 33. Therefore, claim 46, which merely recites that would could incorporate a delayed release coating, does not make up for the deficiencies of Griffin and claim 46 is not obvious over the combination of Griffin and Jordan.

GB 800 973 to Sterling and U.S. Patent No. 4,322,433 to Leslie

GB 800 863 describes a two component drug delivery device. There is no disclosure of anything resembling an immediate release, effervescent coating containing the first agent to be released. U.S. Patent No. 4,322,433 to Leslie fails to make up for this. Leslie leads one skilled in the art to formulations containing drug such as nitroglycerine which readily dissolves in the absence of any coatings or additives, for *delivery to the skin, i.e., percutaneous delivery (see abstract)*. Accordingly, claim 44 and dependent claims are not obvious over GB in combination with Leslie.

GB 800 973 also fails to describe a second component with is either chewable or provides sustained release. Leslie also fails to make up for this deficiency, nor would either lead one skilled in the art to make such a modification to what is disclosed in GB 800 973, as claimed. GB 800 973 discloses only immediate release formulations, and emphasizes the need for rapid release, thereby teaching away from a sustained release formulation. Leslie describes formulations containing lipophilic carriers for transdermal or percutaneous delivery. Although

these may provide sustained release, one skilled in the art would never combine a transdermal formulation with an oral formulation. According, claims 33 and 55, and claims dependent thereon, are not obvious from GB 800 973 alone or in combination with Leslie.

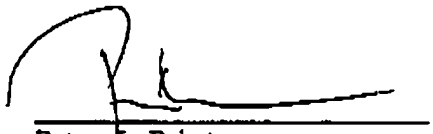
Double Patenting Rejection

Claims 33, 35, 38-39, 41, 43, 44, 46, and 48 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 5, 6, 8, 10, and 16 of Application Serial No. 10/015,930 to Hirsch, *et al.*

Applicants will file a Terminal Disclaimer once claims have been found to be otherwise allowable.

Allowance of claims 33-57, as amended, is respectfully solicited.

Respectfully submitted,



Patrea L. Pabst
Reg. No. 31,284

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HOLLAND & KNIGHT LLP
One Atlantic Center, Suite 2000
1201 West Peachtree Street
Atlanta, Georgia 30309-3400
(404) 817-8473
(404) 817-8588 (Fax)